UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/786,720	02/26/2004	Margot Mary O'Toole	WYE-030	2740

54623 7590 08/29/2006

KIRKPATRICK & LOCKHART NICHOLSON GRAHAM LLP/WYETH
STATE STREET FINANCIAL CENTER
ONE LINCOLN STREET
BOSTON, MA 02111-2950

EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 08/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/786,720	O'TOOLE ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *5 and 10-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-9,19 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/12/05, 4/8/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, methods for detecting polynucleotides and the election of the SFRP1 gene, in the reply filed on June 30, 2006 is acknowledged. The response states that applicants "traverse the non-allowance of the linking claims, including claims 1-4, 6-9, 19 and 20, which are not limited to a single gene or combination of genes" and "traverse the non-allowance of the linking claims 1-9, 19 and 20, which are not limited to detection of polynucleotides." The response does not specifically state the grounds for traversal. For the reasons set forth below, the linking claims are not allowable, and thereby the restriction between the distinct genes and the distinct target molecules is maintained.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-4, 6-9, 19 and 20 have been examined herein. Claim 5 is withdrawn from consideration because this claim is drawn to methods which detect a non-elected gene (i.e., one of the genes from Table 5b). Claims 10-18 are also withdrawn from consideration as being drawn to a non-elected invention.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6-9, 19 and 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a) methods for determining an

expression profile in a mouse wherein the methods comprise: i) obtaining a kidney tissue sample from a control, lupus nephritis (LN)- free mouse and a test mouse; ii) determining the level of SFRP1 (SEQ ID NO: 15) mRNA in the control LN-free mouse and in the test mouse; iii) comparing the level of SFRP1 (SEQ ID NO: 15) mRNA in the control LN-free mouse and in the test mouse, and iv) determining that the test mouse has an increased likelihood of having LN if the test mouse has an increase in SFRP1 (SEQ ID NO: 15) mRNA as compared to the control, LN-free mouse, and b) for methods comprising: i) contacting a LN-affected or LN-predisposed mouse kidney cell or mouse with a test agent; ii) determining the level of SFRP1 (SEQ ID NO: 15) mRNA in said kidney cell or in a kidney cell of said mouse; iii) comparing the level of SFRP1 (SEQ ID NO: 15) mRNA in said kidney cell or in said kidney cell of said mouse after said contacting to the level of SFRP1 (SEQ ID NO: 15) mRNA prior to said contacting; and iv) determining that said agent modulates mRNA expression in said kidney cell or said kidney cell of said mouse if there is a decrease in the level of SFRP1 (SEQ ID NO: 15) mRNA after said contacting step as compared to prior to said contacting step, does not reasonably provide enablement for methods for detecting the expression profile of or monitoring the effect of an agent on any gene that is differentially expressed in any pre-symptomatic lupus-affected or predisposed tissue in any organism. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

Claims 1-4 and 6-9 are drawn to methods for detecting an expression profile of a gene in a biological sample comprising the step of comparing the gene expression profile of a gene in a biological sample to that of a reference expression profile, wherein the gene is differentially expressed in pre-symptomatic lupus- affected or pre-disposed tissues as compared to disease-free tissues. Claims 19 and 20 are drawn to methods comprising contacting a lupus-affected or lupus-predisposed cell or subject with an agent, and comparing the expression profile of a gene before and after said contacting step, wherein said gene is differentially expressed in pre-symptomatic lupus- affected or pre-disposed tissues as compared to disease-free tissues.

Claims 1-3, 6-9 and 19-20 as broadly written encompass the detection of any gene that is differentially expressed in pre-symptomatic lupus- affected or pre-disposed tissues as compared to disease-free tissues. These claims encompass a potentially significantly large genus of genes wherein the gene is defined only in terms of its functional activity (i.e., gene expression pattern), but is not defined in terms of its structural properties.

Claims 1-4, 6-9, 19 and 20 encompass methods for the detection of differentially expressed genes from any biological sample – e.g. urine, sweat, feces, saliva, brain tissue, tears etc. and extracellularly derived mRNAs from serum or plasma.

Claims 1-4, 6-9, 19 and 20 further encompass methods for the detection of genes differentially expressed in any organism – e.g., human, monkey, panda, elephant, rabbit, frog etc.

Claims 1-4, 6-9, 19 and 20 also encompass methods in which the reference expression profile is undefined and in which differential expression may be compared to any disease-free tissue (e.g., a tissue free of cancer, free of viral infection etc).

Claims 1-4, and 6-9 recite the phrase "to detect or monitor an autoimmune disease in said subject." While the claims do not recite an active process step of detecting an autoimmune disease, this phrase, read in light of the specification, has been interpreted as meaning that the information obtained by comparing the expression profile is to be used to detect or monitor an autoimmune disease. The claims do not set forth a particular autoimmune disease and thereby include methods in which the expression profile can be used to monitor any of the physiologically and etiologically diverse autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, type I diabetes mellitus, psoriasis, scleroderma, and autoimmune thyroid disease.

Claims 19 and 20 further encompass methods in which a cell or subject having or predisposed to lupus is contacted with an agent and the effect of the agent on gene expression is monitored before and after the contacting step. As set forth in the

specification, the purpose of such a methodology is to identify agents useful in the treatment of lupus.

Nature of the Invention

The claims encompass methods for detecting an expression profile of a gene that is differentially expressed in pre-symptomatic lupus affected or predisposed tissue as compared to disease free tissues. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Teachings in the Specification and State of the Art:

The specification teaches the results of an expression profiling assay in which mRNA levels in kidney tissues from 4 strains of mice were analyzed. The mice strains analyzed were: MRL/MpJ-Fas^{lpr}, MRL/MpJ, C57BL6, and C57BL6/Fas^{lpr}. The phenotypes of these mice are set forth on pages 2-3 of the specification. A comparison of mRNA levels from kidneys of "pre-symptomatic mice" (described in the specification as including MRL/MpJ mice of 8 weeks or younger) with mRNAs from kidneys of disease-free mice (described in the specification as including C57BL6, and C57BL6/Fas^{lpr} mice) identified mRNAs differentially expressed in pre-symptomatic lupus-affected tissues (see page 69 of the specification). A comparison of mRNA levels from kidney tissues of MRL/MpJ-Fas^{lpr} mice 8 weeks or younger and MRL/MpJ mice 20 weeks or older with C57BL6 and C57BL6/Fas^{lpr} mice (disease-free mice) identified mRNAs differentially expressed in early-stage lupus affected tissues. A comparison of

mRNA levels from kidneys of MRL/MpJ-Fas^{lpr} mice 16 weeks or older with C57BL6 and C57BL6/Fas^{lpr} mice (disease-free mice) identified mRNAs differentially expressed in late disease lupus-affected tissues. Table 4 provides a list of 14 genes that are over-expressed in kidney tissues from "pre-symptomatic" "early disease" and "late disease" mice, as compared to lupus-free mice. Table 4 also lists 11 genes that are over-expressed in "pre-symptomatic" and "early disease", as compared to lupus-free mice. Table 5 lists a number of genes that are under-expressed in lupus-affected kidney tissue as compared to lupus-free kidney tissue of mice.

With respect to the elected invention, the specification teaches that SFRP1 mRNA is increased in kidney tissue from "pre-symptomatic" "early disease" and "late disease" mice as compared to lupus-free mice.

The specification, however, does not teach: (i) the level of expression of the SFRP1 gene or other genes in non-kidney tissues; (ii) the level of expression of the SRFP1 gene or other these genes in tissues from organisms other than mice; or (iii) an association between the level of expression of SFRP1 or other genes and autoimmune diseases other than lupus.

The Predictability or Unpredictability of the Art and Degree of Experimentation:

The art of determining an association between gene expression levels and the occurrence of a disease is highly unpredictable. Knowledge that expression of a gene is associated with a disease such as lupus in one organism (i.e., mice) does not allow one to conclude that expression of this gene is also associated with lupus in other animals, such as humans, cats, dogs, pandas, elephants etc. In the absence of

information regarding the functional properties of the mRNAs and encoded proteins and their role in lupus, it is unpredictable as to whether the SFRP1 gene or other genes will also be present in other mammals and will be expressed at an increased level in other mammals displaying the lupus phenotype.

The post-filing date art corroborates the unpredictability of extrapolating the results of gene expression studies performed in one organism to other organisms, such as humans. For example, Coleman (Drug Discovery Today. 2003. 8: 233-235) found that gene expression patterns between mice and humans shared some degree of similarity, but that the basic patterns of gene expression differed and that there was no general rule for predicting gene expression (page 234). Coleman concluded that '(t)he validity of mouse or other animal species as a human surrogate should not be assumed." These teachings of Coleman support the finding that there is no predictable means for determining whether the gene expression profile obtained in a human will be identical to that in the diverse genus of mammals encompassed by the claims.

Further, Liu et al (Clinical Immunology. 2004. 112: 225-230) studied gene expression in T lymphocytes in human autoimmune disease and murine models of autoimmune disease, including SLE. Liu (see abstract) reported that "we found very little overlap in the gene expression profile between human autoimmune disease and murine models of autoimmune disease and between different murine autoimmune models." Only 2 out of 129 genes differentially expressed in human SLE were also found to be differentially expressed in animal models of SLE/autoimmune disease (see page 228).

Additionally, Liu (page 228) reported that while a conserved gene expression profile was detected in lymphocytes of humans with autoimmune disease, the profile was also seen in unaffected first-degree relatives. This finding of Liu further highlights the unpredictability of using the presence or absence of gene expression profiles to diagnose SLE in the general human population and in non-human mammals.

Secondly, the specification provides information regarding the expression of SRFP1 and other genes only in mouse kidney tissues. It is also unpredictable as to what other types of samples may be assayed for gene expression in order to diagnose lupus or other autoimmune diseases. Modification of gene expression may occur in all cells or may occur in only a subset of cells that are directly involved in a disease. In diseases such as lupus, it is expected that an alteration in gene expression may occur only in those cells / tissues involved in the pathogenesis or effects of lupus. Further, normal expression of a gene in some types of biological samples, such as tears and saliva, may not be at sufficient levels to allow for the identification of a change in gene expression. There is also no disclosure in the specification of methods in which extracellular SFRP1 mRNA or other mRNAs are detected in serum or plasma samples. It is highly unpredictable as to whether SFRP1 is released into the serum or plasma of lupus patients and/or whether there is an increase in the level of extracellular SFRP1 mRNAs or other mRNAs in lupus patients as compared to control patients. One cannot determine *a priori* which cells or other types of biological samples will show an altered gene expression that can be used to diagnose a disease. Such information can only be obtained through experimentation.

Thirdly, the claims encompass methods in which the expression profile can be used to detect or monitor any autoimmune diseases. Thereby, the claims encompass detecting or monitoring autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, type I diabetes mellitus, psoriasis, scleroderma, and autoimmune thyroid disease it is highly unpredictable as to whether the results obtained in kidney samples from mouse models of lupus can be extrapolated to other diseases or disease models. Autoimmune diseases differ significantly with respect to their etiology and symptomology. It is thereby highly unpredictable as to whether SFRP1 mRNAs or other mRNAs which are over-expressed or under-expressed in kidneys of mice having a lupus phenotype will also be over-expressed or under-expressed in humans and other organisms having non-lupus autoimmune diseases.

Fourth, while the specification teaches 14 genes that are over-expressed in kidney tissues from "pre-symptomatic" "early disease" and "late disease" mice, as compared to lupus-free mice and 11 genes that are over-expressed in "pre-symptomatic" and "early disease", as compared to lupus-free mice (see Table 4), this disclosure is not considered to be representative of the broadly claimed genus of any gene that is differentially expressed in "pre-symptomatic lupus-affected or –predisposed tissues as compared to disease-free tissues." The claims do not define the gene to be monitored in terms of any particular structural properties and thereby the claims include a potentially significantly large genus of genes that have not yet been identified or that have not yet been characterized as being associated with lupus. The art of identify genes that are associated with a disorder as complex as lupus and using those genes

to detect or monitor lupus or to identify agents that could be used to treat lupus is highly unpredictable. The finding that a gene, such as SFRP1, is over-expressed in mouse models having lupus does not allow one to reasonably predict the structure of other genes that will have similar expression patterns and which could be used to monitor or detect lupus or identify agents for treating lupus.

Working Examples

Again, with respect to the elected invention, the specification teaches that SFRP1 mRNA is increased in kidney tissue from "pre-symptomatic" "early disease" and "late disease" mice as compared to lupus-free mice.

The specification does not provide any working examples in which lupus is detected or monitored in any non-mouse organism.

The specification does not provide any working examples in which gene expression is analyzed in an autoimmune disease other than lupus, in a biological sample other than a kidney sample.

The specification does not provide any working examples in which gene expression is analyzed in a biological sample other than a kidney tissue sample.

The specification does not provide any working examples in which gene expression is analyzed by comparing gene expression in a biological sample to a reference expression profile other than an expression profile from a subject that does not have lupus.

Amount of Direction or Guidance Provided by the Specification:

The specification does not provide any specific guidance as to how to predictably identify additional mammals whose expression of SLRP1 is correlated with lupus. The specification does not teach the existence of homologues of SLRP1in a representative number of other mammals. There is also insufficient information regarding the functional activity of SLRP1 and the other genes recited in Tables 4 and 5a as it relates to the cause or occurrence of lupus to allow one to conclude that these genes have a similar functional role in contributing to the development of lupus in other organisms. There are no teachings in the specification regarding the fact that a representative number of mammals (including, e.g., whales, pandas, elephants etc) develop lupus with characteristics that are sufficiently similar to those in the mouse model and in humans so that one could reasonably conclude that the effects of an alteration in gene expression in other mammals would be similar to that observed in mice. The teachings of Liu support this unpredictability in that Liu (page 220, column 2) teaches that "(o)ur results indicate that murine models do not perfectly model their corresonding human autoimmune diseases when gene expression profiles are considered. Other investigators have previously recognized limiations of using rodent models to study human diseases." No specific guidance is provided in the specification as to how to predictably identify additional mammals which manifest SLE in a manner sufficiently similar to humans so as to indicate that the gene expression profile of such mammals would be the same as that of humans having SLE.

While methods for expression profiling are known in the art, such methods provide only the general guidelines that allow researchers to randomly search for genes

whose expression may linked to a disorder, such as SLE or NL. The results of performing such methodology is highly unpredictable. The specification has provided only an invitation to experiment. The specification does not provide a predictable means for identifying additional mammals which can be diagnosed for lupus by detecting SFRP1 mRNA levels or a predictable means for identifying additional cell types and samples which show an increase in SFRP1 mRNA levels. The specification also does not provide sufficient guidance to allow one to extrapolate the findings regarding the mouse lupus model to other autoimmune diseases.

Further, the specification does not provide any specific guidance as to how to predictably make and use variants of SFRLP1 or other genes in order to identify additional genes differentially expressed in pre-symptomatic lupus-affected or predisposed tissues. While one could generate a significantly large genus of nucleic acids in which nucleotides of any identity are added, deleted or substituted within the sequence of SFRLP1, and while one could generate a genus of any nucleic acid from any organism, and then assay each of the nucleic acids to try to determine their biological activity or expression pattern, such trial-by-error experimentation is considered to be undue. Providing methods for searching for additional nucleic acids and trying to determine the function of the resulting nucleic acid or trying to establish an association between the nucleic acids and lupus or other autoimmune diseases is not equivalent to teaching how to make and use specific nucleic acids which are differentially expressed in pre-symptomatic lupus-affected or predisposed tissues.

Conclusions:

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the claims do not bear a reasonable correlation to the scope of enablement because the specification teaches an association between the expression of SFRP1 mRNA levels in kidney tissue samples obtained from mice having a lupus phenotype and in control mice, but does not teach an association between the expression of SFRP1 in a representative number of additional organisms or cell or tissue types. The specification also does not teach a representative number of genes that are differentially expressed in "pre-symptomatic lupus-affected or –predisposed tissues as compared to disease-free tissues." The specification also does not teach a representative number of autoimmune diseases which could be detected or monitored by assaying for the expression of SFRP1 or other genes. Accordingly, in view of the unpredictability in the art, and the lack of disclosure in the specification and in the prior

art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

3. Claims 1-3, 6-9, 19 and 20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 1-3 and 6-9 are drawn to methods for detecting an expression profile of a gene in a biological sample comprising the step of comparing the gene expression profile of a gene in a biological sample to that of a reference expression profile, wherein the gene is differentially expressed in pre-symptomatic lupus- affected or pre-disposed tissues as compared to disease-free tissues. Claims 19 and 20 are drawn to methods comprising contacting a lupus-affected or lupus-predisposed cell or subject with an agent, and comparing the expression profile of a gene before and after said contacting step, wherein said gene is differentially expressed in pre-symptomatic lupus- affected or pre-disposed tissues as compared to disease-free tissues.

The specification teaches the results of an expression profiling assay in which mRNA levels in kidney tissues from 4 strains of mice were analyzed. Table 4 provides a list of 14 genes that are over-expressed in kidney tissues from "pre-symptomatic" "early disease" and "late disease" mice, as compared to lupus-free mice. Table 4 also lists 11 genes that are over-expressed in "pre-symptomatic" and "early disease", as compared to lupus-free mice. Table 5 lists a number of genes that are under-expressed in lupus-

affected kidney tissue as compared to lupus-free kidney tissue of mice. In particular, the specification teaches that SFRP1 mRNA is increased in kidney tissue from "pre-symptomatic" "early disease" and "late disease" mice as compared to lupus-free mice.

The SEQ ID Nos. for nineteen of the genes differentially expressed in the mouse lupus model are set forth in Table 1. Accordingly, methods for detecting the genes of SEQ ID NO: 1-29, and in particular, methods for detecting the SFRP1 gene of SEQ ID NO: 15 meet the written description requirement.

However, the claims as broadly written are not limited to genes of a specific identity or structure. Rather, the claims broadly encompass the detection of any gene that is differentially expressed in any pre-symptomatic lupus-affected or –predisposed tissue and/or any early-stage-affected tissue.

Many of the genes set forth in Tables 4 and 5a are defined only in terms of a "qualifier." Further, the claims encompass genes of any identity that are differentially expressed in any predisposed or presymptomatic lupus-affected tissue. The specification indicates that the claimed invention is intended to encompass the detection of genes that share an unstated level of sequence identity with the identified genes, homologues of said genes and genes which contain mutations (insertions, deletions or additions or gross rearrangements) of the identified gene (see, for instance, pages 18, 19 and 21). These genes may have functional activities similar to or distinct from the genes set forth in Table 4 and 5a.

. Accordingly, the claims are inclusive of methods which detect genes which have distinct biological activities from the nucleic acids of SEQ ID NO: 1-29.

The general knowledge in the art concerning homologues, mutants, allelic and splice variants does not provide any indication of how modification of the sequence of SEQ ID NO: 1 will effect the functional properties of SEQ ID NO: 1. The structure and function of one molecule does not provide guidance as to the structure and function of other molecules. Therefore, the description of one molecule (SEQ ID NO: 1-29) is not representative of the broadly claimed genus of homologues, splice, mutant and allelic variants of SEQ ID NO: 1-29 or of the other broadly claimed genes of Tables 4 or 5a or of the broadly claimed genus of any gene differentially expressed in any predisposed or presymptomatic lupus-affected tissue. A general statement in the specification of a desire to obtain gene sequences, homologues from other species, mutated species, SNPs, polymorphic sequences, novel gene sequences is not equivalent to providing a clear and complete description of specific sequences which fall within the claimed genus of genes.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a

nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

Additionally, Applicants' attention is directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In the instant application, because the claims define the genes only in terms of their functional properties (i.e., expression properties), one of skill in the art cannot envision the detailed chemical structure of the genes encompassed by the claimed methods, regardless of the complexity or simplicity of the method of identification. Adequate written description requires more than a mere statement that analysis of such nucleic acids are part of the invention and reference to a potential method for identification. The particular nucleic acids are themselves required.

In conclusion, the limited information provided in the specification is not deemed sufficient to reasonably convey to one of skill in the art that Applicants were in possession of the claimed genus of any gene differentially expressed in any predisposed or presymptomatic lupus-affected tissue. Therefore, the written description

requirement has not been satisfied for the claims as they are broadly written. Applicants attention is drawn to the Guidelines for the Examination of Patent Applications under 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 6-9, 19 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-4, 6-9, 19 and 20 are indefinite over the recitations of "lupus-affected," "early-stage lupus affected," "predisposed tissues" and "disease-free tissues." Regarding "predisposed tissues," it is unclear as to what the tissues are predisposed to – e.g., lupus, any autoimmune disease, or any disease or condition. It is further unclear as to whether a predisposed tissue is any tissue from a subject predisposed to developing lupus (i.e., a subject with a family history of lupus) or if a predisposed tissue is any tissue that would be affected by lupus, e.g., a kidney tissue. Similarly, it is unclear as whether lupus-affected and early-stage lupus affected tissues include any tissues obtained from a subject having lupus or early-stages of lupus, or includes only tissues from patients having lupus that are directly (e.g., morphologically or functionally) affected by the occurrence of lupus, or includes tissues from any subjects (including control subjects) wherein it is a property of the tissues that they would be effected by the occurrence of lupus or early-stages of lupus. It is also unclear as to whether the

disease-free tissues are from a subject that is free of symptoms of lupus or any autoimmune disease or any and all other diseases or from a tissue of any subject wherein the tissue does not show signs or symptoms or is unaffected by lupus, any autoimmune disease or any and all other diseases. Additionally, claims 19 and 20 are indefinite over the recitation of "disease-free tissues" (claim 19) and "disease-free kidney tissues" (claim 20). It is as to whether the disease-free tissues are from a subject that is free of symptoms of lupus or any autoimmune disease or any and all other diseases or from a tissue of any subject wherein the tissue does not show signs or symptoms or is unaffected by lupus, any autoimmune disease or any and all other diseases.

Claims 2-4 and 6-9 are indefinite because it is unclear as to how the limitation of "wherein at least one gene is differentially expressed in early-stage lupus as compared to disease-free tissues." It is unclear, for example, as to whether this is a property of the gene in addition to the fact that the gene is differentially expressed in pre-symptomatic lupus-affected or predisposed tissues or whether the reference to the fact that the gene is expressed in early-stage lupus-affected tissues further defines either the pre-symptomatic lupus-affected or the predisposed tissues.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140

F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3, 6-9 and 19-20 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 5-8 and 22 of copending Application No. 10/686,619. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims and the claims of '619 are both inclusive of methods comprising i) determining the expression of a gene in a kidney sample, wherein the gene is expressed at an elevated level in a mammal that has an increased likelihood of lupus nephritis, and ii) comparing the level of expression of said gene to a reference expression level in a control sample. The claims of '619 differ from the present claims in that the claims of '619 specify that the gene is a midkine gene, while the present claims allow for the detection of any gene differentially expressed in pre-symptomatic lupus-affected or lupus-predisposed tissues as compared to disease-free tissues. In the absence of evidence to the contrary, the midkine gene set forth in the claims of '619 is encompassed by the presently claimed genus of genes differentially expressed in pre-symptomatic lupus-affected or lupus-predisposed tissues set forth in the present claims.

Further, the present claims (e.g., claims 6 and 9) and the claims of '619 both encompass the analysis of gene expression in human tissues, and particularly human kidney tissues. With respect to claims 19 and 20, the claims of '619 do not specify that the expression level is determined after contacting a cell or subject with an agent. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods of '619 so as to have contacted a test cell or test subject with an agent prior to assaying for the level of gene expression in order to have monitored the effect of treatment on gene expression and/or on the occurrence or progression of lupus.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4, and 6-9 are rejected under 35 U.S.C. 102(e) as being anticipated by Lorenz (U.S. Patent No. 6,706,867).

Lorenz (see paragraphs 76, 103, 105, 107, Example 2 and Table 1) teaches methods comprising detecting an expression profile of a SFRP1 gene in a biological sample from a subject and comparing said expression profile to a reference expression profile of a SFRP1 gene. It is a property of the SFRP1 gene that this gene is differentially expressed in pre-symptomatic lupus-affected and predisposed tissues and in early-stage lupus affected tissues as compared to disease-free tissues. Regarding the recitation in claims 1-4, and 6-9 of "comparing...to detect or monitor an autoimmune disease in said subject," the claims do not recite an active process step of detecting or monitoring an autoimmune disease and the claims are not drawn to methods for detecting or monitoring an autoimmune disease. The claims merely state a characterization or conclusion of the results of the step of comparing. Therefore, the "to detect or monitor an autoimmune disease in said subject" clause is not considered to further limit the method defined by the claim and has not been given weight in construing the claims. See Texas Instruments, Inc. v. International Trade Comm., 988 F.2d 1165, 1171, 26 USPQ2d 1018, 1023 (Fed Cir. 1993) ("A 'whereby' clause that merely states the result of the limitations in the claim adds nothing to the patentability or substance of the claim."). See also Minton v. National Assoc. of Securities Dealers, Inc., 336 F.3d 1373, 1381, 67 USPQ2d 1614, 1620 (Fed. Cir. 2003) ("A whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited.").

Regarding claim 6, Lorenz teaches that the biological sample is obtained from a human subject (see paragraph 68).

Regarding claim 7, as stated above the phrase "to detect or monitor an autoimmune disease" is not considered to be an active process step and is not considered to further limit the claim. Thereby, the recitation in claim 7 that the autoimmune disease (i.e., the disease to be detected) is LN or SLE also is not considered to further limit the claim.

Regarding claim 8, Lorenz (paragraphs 50 and 53) teaches analyzing the expression profiles using a method of RT-PCR to amplify the nucleic acids present in the biological sample.

Regarding claim 9, it is a property of the SFRP1 gene that this gene is differentially expressed in pre-symptomatic and early-stage lupus affected kidney tissue as compared to disease-free kidney tissue.

7. Claims 1-4, 6, 7 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Ugolini (Oncogene. 2001. 20: 5810-5817).

Ugolini teaches methods comprising the steps of detecting an expression profile of a SFRP1 gene in a biological sample from a subject and comparing said expression profile to a reference expression profile of a SFRP1 gene (see page 5816 and Figures 1 and 2). It is a property of the SFRP1 gene that this gene is differentially expressed in pre-symptomatic lupus-affected and predisposed tissues and in early-stage lupus affected tissues as compared to disease-free tissues. Regarding the recitation in claims 1-4, 6, 7 and 9 of "comparing...to detect or monitor an autoimmune disease in said subject," the claims do not recite an active process step of detecting or monitoring an autoimmune disease and the claims are not drawn to methods for detecting or

monitoring an autoimmune disease. The claims merely state a characterization or conclusion of the results of the step of comparing. Therefore, the "to detect or monitor an autoimmune disease in said subject" clause is not considered to further limit the method defined by the claim and has not been given weight in construing the claims. See Texas Instruments, Inc. v. International Trade Comm., 988 F.2d 1165, 1171, 26 USPQ2d 1018, 1023 (Fed Cir. 1993) ("A 'whereby' clause that merely states the result of the limitations in the claim adds nothing to the patentability or substance of the claim."). See also Minton v. National Assoc. of Securities Dealers, Inc., 336 F.3d 1373, 1381, 67 USPQ2d 1614, 1620 (Fed. Cir. 2003) ("A whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited.").

Regarding claim 6, Ugolini teaches that the biological sample is obtained from a human subject (see page 5815).

Regarding claim 7, as stated above the phrase "to detect or monitor an autoimmune disease" is not considered to be an active process step and is not considered to further limit the claim. Thereby, the recitation in claim 7 that the autoimmune disease (i.e., the disease to be detected) is LN or SLE also is not considered to further limit the claim.

Regarding claim 9, it is a property of the SFRP1 gene that this gene is differentially expressed in pre-symptomatic and early-stage lupus affected kidney tissue as compared to disease-free kidney tissue.

8. Claims 1-3, 6, 7, 9 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Rider et al (Clinical Immunology and Immunopathology. 1998. 89: 171-180).

Rider teaches methods comprising the steps of detecting an expression profile of a calcineurin gene in a biological sample from a subject having lupus and comparing said expression profile to a reference expression profile of a calcineurin gene from a control subject (see page 172).

Since the claims define the gene in terms of its functional properties, but do not recite a particular chemical structure for the gene, and because expression of the calcineurin gene is associated with lupus, in the absence of evidence to the contrary, it is considered to be a property of the calcineurin gene that this gene is differentially expressed in pre-symptomatic lupus-affected and predisposed tissues and in early-stage lupus affected tissues as compared to disease-free tissues. Regarding the recitation in claims 1-3, 6, 7 and 9 of "comparing...to detect or monitor an autoimmune disease in said subject," the claims do not recite an active process step of detecting or monitoring an autoimmune disease and the claims are not drawn to methods for detecting or monitoring an autoimmune disease. The claims merely state a characterization or conclusion of the results of the step of comparing. Therefore, the "to detect or monitor an autoimmune disease in said subject" clause is not considered to further limit the method defined by the claim and has not been given weight in construing the claims. See Texas Instruments, Inc. v. International Trade Comm., 988 F.2d 1165, 1171, 26 USPQ2d 1018, 1023 (Fed Cir. 1993) ("A 'whereby' clause that merely states the result of the limitations in the claim adds nothing to the patentability or

substance of the claim."). See also Minton v. National Assoc. of Securities Dealers, Inc., 336 F.3d 1373, 1381, 67 USPQ2d 1614, 1620 (Fed. Cir. 2003) ("A whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited.").

Regarding claim 6, Rider teaches that the biological sample is obtained from a human subject (see page 172).

Regarding claim 7, as stated above the phrase "to detect or monitor an autoimmune disease" is not considered to be an active process step and is not considered to further limit the claim. Thereby, the recitation in claim 7 that the autoimmune disease (i.e., the disease to be detected) is LN or SLE also is not considered to further limit the claim.

Regarding claim 9, in the absence of evidence to the contrary, it is considered to be a property of the calcineurin gene that this gene is differentially expressed in pre-symptomatic and early-stage lupus affected kidney tissue as compared to disease-free kidney tissue.

Regarding claim 19, Rider teaches a method comprising contacting lupus-affected cells with an agent (i.e., estrogen), and comparing the expression of calcineurin before (i.e., untreated cells) and after said contacting to determine whether the agent modulates expression of calcineurin (see pages 172-173 and Figure 3).

9. Claims 1-4, and 6-9 are rejected under 35 U.S.C. 102(a) as being anticipated by Ijiri (Journal of Rheumatology. 2002. 29: 2266-2270).

Ijiri teaches methods comprising the steps of detecting an expression profile of a SFRP1 gene in a biological sample from a subject and comparing said expression profile to a reference expression profile of SFRP1 gene (see abstract and page 2267). It is a property of the SFRP1 gene that this gene is differentially expressed in pre-symptomatic lupus-affected and predisposed tissues and in early-stage lupus affected tissues as compared to disease-free tissues. Regarding the recitation in claims 1-4 and 6-9 of "comparing...to detect or monitor an autoimmune disease in said subject," the claims do not recite an active process step of detecting or monitoring an autoimmune disease and the claims are not drawn to methods for detecting or monitoring an autoimmune disease. The claims merely state a characterization or conclusion of the results of the step of comparing. Therefore, the "to detect or monitor an autoimmune disease in said subject" clause is not considered to further limit the method defined by the claim and has not been given weight in construing the claims. See Texas Instruments, Inc. v. International Trade Comm., 988 F.2d 1165, 1171, 26 USPQ2d 1018, 1023 (Fed Cir. 1993) ("A 'whereby' clause that merely states the result of the limitations in the claim adds nothing to the patentability or substance of the claim."). See also Minton v. National Assoc. of Securities Dealers, Inc., 336 F.3d 1373, 1381, 67 USPQ2d 1614, 1620 (Fed. Cir. 2003) ("A whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited.").

Regarding claim 6, Ijiri teaches that the biological sample is obtained from a human subject (see pages 2266-2267).

Regarding claim 7, as stated above the phrase "to detect or monitor an autoimmune disease" is not considered to be an active process step and is not considered to further limit the claim. Thereby, the recitation in claim 7 that the autoimmune disease (i.e., the disease to be detected) is LN or SLE also is not considered to further limit the claim.

Regarding claim 8, Ijiri (page 2267) teaches analyzing the expression profiles using a method of RT-PCR to amplify the nucleic acids present in the biological sample.

Regarding claim 9, it is a property of the SFRP1 gene that this gene is differentially expressed in pre-symptomatic and early-stage lupus affected kidney tissue as compared to disease-free kidney tissue.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ugolini in view of Lorenz.

The teachings of Ugolini are presented above. In particular, Ugolini teaches analyzing SFRP1 gene expression using Northern blotting techniques, but does not teach analyzing SFRP1 gene expression using an RT-PCR assay.

However, Lorenz (paragraphs 50 and 53) teaches methods of gene expression analysis. Specifically, Lorenz teaches that RNAs from biological samples may be amplified by RT-PCR prior to microarray analysis in order to increase the quantity of the target nucleic acid, thereby increasing the sensitivity and specificity of the expression analysis.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Ugolini so as to have amplified the SFRP1 mRNA using RT-PCR prior to probe hybridization analysis in order to increase the quantity of the target SFRP1 nucleic acids, thereby increasing the sensitivity and specificity of the method for analyzing SFRP1 expression.

11. Claims 8 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rider in view of Lorenz.

The teachings of Rider are presented above.

Regarding claim 8, Rider teaches analyzing calcineurin gene expression using RNAse protection assays, but does not teach analyzing calcineurin gene expression using an RT-PCR assay.

However, Lorenz (paragraphs 50 and 53) teaches methods of gene expression analysis. Specifically, Lorenz teaches that RNAs from biological samples may be amplified by RT-PCR prior to microarray analysis in order to increase the quantity of the target nucleic acid, thereby increasing the sensitivity and specificity of the expression analysis.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Rider so as to have amplified the calcineurin mRNA using RT-PCR prior to probe hybridization analysis in order to increase the quantity of the target calcineurin nucleic acids, thereby increasing the sensitivity and specificity of the method for analyzing calcineurin expression.

Regarding claim 20, Rider teaches methods for analyzing the expression of calcineurin in biological samples obtained from lupus patients receiving prednisone (see page 172). Rider teaches a method comprising contacting lupus-affected cells with an agent (i.e., estrogen), and comparing the expression of calcineurin before (i.e., untreated cells) and after said contacting to determine whether the agent modulates expression of calcineurin (see pages 172-173 and Figure 3). However, Rider does not teach methods for monitoring changes in gene expression wherein calcineurin gene expression prior to contacting the patient with prednisone is compared to calcineurin gene expression following contacting the patient with prednisone.

However, Lorenz (e.g., paragraph 8) teaches methods for analyzing gene expression in a subject that has been administered a drug and teaches monitoring the effect of a drug by assaying for a change in the level of gene expression.

In view of the teachings of Lorenz, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Rider so as to have analyzed calcineurin gene expression prior to and following administration of estradiol to lupus-affected patients in order to more accurately analyze the effect of estradiol on calcineurin gene expression in vivo.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571)-272-0735.

The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866)-217-9197 (toll-free).

Carla Myers
August 22, 2006

CARLA J. MYERS
PRIMARY EXAMINER